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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/370,453	08/09/1999	DAN W. DENNEY JR.	GENITOPE-038	8128

23535 7590 04/20/2005

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/370,453	DENNEY, DAN W.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 25-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 9, 2005 has been entered.

Please note that the examiner assigned to this application has changed.

Claims 25, 28 and 29 have been amended. Claims 30-32 have been canceled. Claims 25-29 are pending and under consideration.

Text of sections of Title 35, U.S. code not found in this action can be found in a previous action.

Acknowledgement is made of applicants claim to an earlier effective filing date through 08/644,664, filed May 1, 1996. After review of the '664 application, no support could be identified for the instant claims which require the specific insertion of Vh and Vl regions into expression vectors. Accordingly, the instant application is given the effective priority date of December 6, 1996.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A). Claims 25, 28 and 29 recite "a multivalent composition for active immunotherapy produced according to a method comprising", however the final step recites

"identifying a transformed cell" or "identifying at least one individual clone". It is unclear how the identification of a cell or a clone relates to the multivalent composition claimed. Particularly, it is unclear if the multivalent composition comprises the one transformed cell, or the one clone, or if the multivalent composition comprises proteins secreted by the one transformed cell or the one clone, or if the multivalent composition is to be made up of a multiplicity of transformed cells, clones, or secreted proteins.

(B) Claim 25, section f), claim 28, section h), claim 29, section h) as well as claims 26 and 27 all recite "said Vh and Vl regions". It is unclear if "said" regions must include at least two V regions which differ by at least one idiotype, in which case the transformed cell or clone has received two copies of a Vl or Vh region which differ by at least one idiotype, or if "said regions" includes one of the two variant V regions which was clonally selected in the transformed cell line. For purpose of examination, all alternatives will be considered.

Claims 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleary et al (Cell, 1986, Vol. 44, pp. 97-106) in view of Levy et al (Journal of Experimental Medicine, 1988, Vol. 168, pp. 475-489) and Embleton et al (Nucleic Acids Research, 1992, Vol. 20, pp. 3831-3837).

Claims 25, 28 and 29 are drawn to a multivalent composition for active idiotype immunotherapy produced by insertion of isolated nucleic acids from malignant B-cell lymphoma into an expression vector, wherein said isolated nucleic acids comprise nucleotide sequences encoding at least one Vh region and at least two Vh regions, nucleotide sequence encoding at least two Vh regions and at least one Vl region or nucleotide sequence encoding at least two Vh regions and at least two Vl regions, wherein said at least two Vh regions and said at least two Vl regions differ by at least one idiotope. Claims 26 and 27 embody the composition of claim 25 wherein the nucleotide sequence encoding said Vh and Vl regions comprise at least two Vh and one Vl region, and at least two Vl and one Vh region, respectively.

Section 2113 of the M.P.E.P. states:

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

It is noted that the instant claims are rejected under 112, 2nd because it is unclear how the final method step produces a multivalent composition. Because of this lack of clarity, the physical and functional character of the multivalent composition itself is uncertain. When given the broadest reasonable interpretation, the multivalent composition reads on a multiplicity of whole antibodies having different idiotopes, a multiplicity of cells expressing or secreting a multiplicity of whole antibodies having different idiotopes, a multiplicity of scFv which differ in idiotopes between the various Vh molecules and between the various Vl molecules that would constitute the multiple scFv, etc.

Cleary et al teach instance of patients whose B cell tumors escaped the therapeutic effects of a monoclonal anti-idiotype antibody because of the emergence of subclones that showed changes in their Ig idiotopes (page 97, second column, lines 36-39) Cleary et al suggest that the idiotype heterogeneity unmasked by the anti-idiotype therapy resulted from somatic mutations within the variable region because the variant subclones were derived from the same original clone of neoplastic B-cells, and the same patterns of bands for rearranged Ig genes were detected (page 97, second column, lines 40-47). To confirm this hypothesis, Cleary et al cloned and sequences the functional heavy chain Ig genes from multiple independent isolates of a patients tumor cell population to conclude that point mutations in the variable regions accounted for the loss of idiotype following antibody therapy (page 97, second column, lines 48-54 and page 103, first column, lines 1-6 under the heading "Discussion"). Cleary et al also teach a marked heterogeneity in the variable region sequences of the tumor cell population prior to anti-idiotype therapy, having significant clustering of amino acid substitutions in CDR2 (page 97, second column, line 54 to page 98, first column, line 3 and page 103, second column, lines 26-28). Cleary et al teach that the clustering of mutation in the CDR2 after anti-idiotype therapy can be attributed in part to the strong negative selection exerted by the 7D11 antibody (page 104, first column, first paragraph). Cleary et al do not teach a multivalent idiotypic vaccine which would comprise the variant Vh sequences which would comprise more than one idiotype and variant Vl sequence which would comprise more than one idiotype.

Levy et al corroborates the teaching of Cleary et al regarding the Vh sequences from multiple isolated of human B cell lymphoma (page 475, lines 19-23) and further teach that the light chain genes of human lymphoma cells mutate independently from heavy chain genes (page 476, lines 7-13).

Embleton et al teach in-cell PCR allowing for the linking and amplification of the expressed Vh and Vl within a single B-lymphocyte in order to preserve the particular combination of Vh and Vl within a lymphocyte (page 3831, second column, lines 17-18). Embleton et al teach that this method is superior to the prior art methods of PCR cloning of Ig regions which lost the natural combination of the heavy and light chains and required artificial recombination which had the potential to be dominated by promiscuous chains leading to different affinities and specificities (page 3831, second column, lines 8-16).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make a multivalent composition for idiotypic vaccination of a patient having a B-cell lymphoma by amplify and link the Vh and Vl chains of a multitude of B-lymphoma cells and recombinatly expressing the recombinant variable chains while retaining the original combinations of heavy and light chains in host cells. One of skill in the art would have been motivated to do so by the teachings of Cleary et al on the emergence of malignant B-cells which escaped anti-idiotype therapy due to somatic mutations with the variable regions and the evidence presented by Cleary regarding the existence of heavy chain heterogeneity before the anti-idiotype therapy; the teachings of Levy et al on the presence of heterogeneity in the light chain of human B-cell lymphomas, and the teachings of Embleton regarding improvements in the PCR cloning of immunoglobulin genes from B-lymphocytes which preserves the natural paring of heavy chain and light chain and avoids the problems associated with the screening of artificial combinations. One of skill in the art would have been motivated to include a multitude of natural combinations of Vh and Vl sequences from the patients B-cell lymphomas in order to insure that an immune response could be raised to more than just one population of B-cells having a specific combination of Vh and Vl sequences because although it is evidence that a single clonal event precipitated the B-cell lymphoma, somatic mutations accumulate within both the heavy and light chains of the lymphoma

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/18/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER